

July 16, 2003

Public Information and Records
Integrity Branch (PIRIB) (7502C), Office of Pesticide Programs (OPP),
Environmental Protection Agency, 1200 Pennsylvania Ave., NW.,
Washington, DC 20460-0001,

Re: Characterization of Atrazine Cancer Epidemiology Data. Meeting of the FIFRA Scientific Advisory Panel. July 17, 2003

Attention: Docket ID Number OPP-2003-0186

Federal Register: May 30, 2003 (Volume 68, Number 104, Notices, Page 32488-32490)

These comments are submitted by regular mail to the above address, and by email to opp-docket@epa.gov

Dear Scientific Advisory Panel members:

These comments are being submitted on behalf of the Natural Resources Defense Council (NRDC) and co-signers. NRDC uses law, science, and the support of more than 500,000 members nationwide to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things. More information is available at our website: www.nrdc.org

INTRODUCTION

In these comments we discuss the available evidence of carcinogenicity for atrazine, and demonstrate that these data fulfill the criteria for classifying atrazine as a “likely” human carcinogen under the 2003 Draft Final cancer guidelines. Although there are sufficient data for such a determination, it is nevertheless concerning that atrazine has never been properly tested for carcinogenicity in a rigorous two-year animal bioassay, despite the fact that atrazine has been under “EPA special review” for almost a decade, and in use commercially for a half-century here in the US. Yet, despite mounting evidence of endocrine disruption and carcinogenicity, the EPA is poised to allow atrazine use to continue. Moreover, EPA is prepared to classify atrazine as “not likely” a human carcinogen despite: a) evidence of cancer in laboratory animals, b) demonstrated endocrine disruption in atrazine-exposed laboratory animals, which may predispose an atrazine-exposed fetus or child to cancer later in life c) evidence that exposure to atrazine during development predisposes laboratory animals to developing cancer later in life, and d) evidence of endocrine and cancer effects in exposed humans. Waiting for definitive epidemiology is, literally, waiting for harmful effects in epidemic proportions. It is the role of EPA to regulate chemicals so as to protect human health and the environment, not commercial interests.

EPA 2003 DRAFT FINAL GUIDELINES FOR CANCER ASSESSMENT: Atrazine fulfills criteria for “likely” human carcinogen

The EPA has released its new Draft Final Guidelines for assessing chemicals for carcinogenicity.¹ Although EPA continues to use the old 1999 Draft guidelines until the 2003 guidelines are finalized. The Scientific Advisory Board (SAB) recommended that the EPA “rapidly” finalize the Guidelines and the Supplemental in their Draft report of June, 2003.² The following criteria from the 2003 Draft Final Guidelines for classifying a chemical as a “likely” human carcinogen are provided below (exact and complete text), and are discussed in these comments with respect to atrazine.

“Likely to Be Carcinogenic to Humans”

This descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor “carcinogenic to humans”. Adequate evidence consistent with this descriptor covers a broad spectrum. Some examples to illustrate the broad range of data combinations that are covered by this descriptor include:

- An agent with some evidence of an association between human exposure and cancer, with or without evidence of carcinogenicity in animals.
- An agent that has tested positive in more than one species, sex strain, site, or exposure route, with or without evidence of carcinogenicity in humans;
- A positive study that indicates a highly significant result, for example, an uncommon tumor, a high degree of malignancy, or an early age at onset;
- A positive study that is strengthened by other lines of evidence, for example, some evidence of an association between human exposure and cancer (but not enough to infer a causal association), or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case; or
- A robust animal tumor response in a single experiment that is assumed to be relevant to humans.

EVIDENCE FOR CARCINOGENICITY IN EXPERIMENTAL ANIMALS: atrazine is tumorigenic in one rat and one mouse strain, and may predispose developmentally-exposed rats to cancer later in life

Atrazine has never been tested for carcinogenicity through an endocrine disruptor mechanism, its most likely mechanism for cancer induction. This would include studies dosing pregnant dams, and then observing the pups for possible cancer progression, studies of continuous exposure for at least 24-30 months, and studies where one group of pups is exposed only during gestation, while siblings are exposed during lactation and throughout their life.

In 1998 the International Agency for Research on Cancer reviewed the available data on atrazine, and determined that there is sufficient evidence in experimental animals for the carcinogenicity of atrazine (IARC Monographs, Volume 73, 1999). This evaluation was based on findings of mammary tumors in intact female Sprague-Dawley (SD) rats. The published studies cited below suggest that response to atrazine is strain and dose dependent. Note, however, that the ability of atrazine to induce endocrine disruption is a common finding throughout the studies. This does not represent disagreement in the published literature, but rather demonstrates the complex action of atrazine, like most endocrine disruptors, on the complex web of hormonal regulation. All results summarized below are of statistical significance, and are reported by the study authors.

- Chronic feeding studies with atrazine revealed early onset mammary tumor and pituitary tumors, associated with a deficient leutenizing hormone (LH) surge, and early or severe estrous cycle disruption.³
- Published data by EPA scientists demonstrate in animal studies that exposure to atrazine during development of Long Evans (LE) rats increases the risk of developing cancer later in life. LE rats were exposed in utero to atrazine, followed by challenge with the carcinogen dimethybenz[a]anthracene.⁴ Atrazine-exposed pups demonstrated delayed mammary bud outgrowth, followed by an increase in multiplicity and volume of tumors

after exposure to the carcinogen, compared to non-atrazine treated controls. In addition, the atrazine-exposed pups showed an increase in organ pathology, compared with controls. The authors suggest that by delaying mammary gland development, gestational atrazine exposure increases the susceptibility of the LE female to carcinogens, perhaps, by extending the period of vulnerability.⁵

- Authors report a statistically significant increase (p-value less than 0.001) of lymphomas (6/30) in a group of 30 male Swiss albino mice “given intraperitoneally 0.25 cc of a 2 ppm solution of atrazine for 13 times every third day to total administration of 0.26 mg of Atrazine/kg of body weight”. Lymphomas arising in control animals was only 1/100. This increase in tumors among treated animals was evident after only one year of atrazine treatment.⁶
- The LE rat strain appears to be more sensitive to atrazine-induced ovarian cycle disruption than the SD strain.⁷ A single dose of atrazine (300 mg/kg) suppressed the estrogen-induced surges of leutenizing hormone (LH) and prolactin in ovariectomized LE, but not SD female rats. This effect was evident at 1 hr after dosing, and persisted past 6 hrs post-dosing;⁸ this is important since LH during gestational day (GD) 7-10 is essential for pregnancy maintenance, and as little as a 2-4 hr deprivation of LH secretion may be sufficient to terminate pregnancy in a rat.⁹
- Short-term atrazine treatment of LE and SD rats demonstrated strain-specific effects, while long-term treatment affected both experimental strains, even at low doses. Three daily doses of atrazine (50, 100, 200 or 300 mg/kg) suppressed estrogen-induced LH and prolactin surges in ovariectomized LE female rats (authors report that this occurs in a dose-dependent manner. The same treatment had no effect on SD rats. At 300 mg/kg the SD rats had suppressed prolactin levels, but LH was not affected. Although strain differences were obvious during short treatments, continued dosing for 21 days resulted in inhibition of LH and prolactin release in both LE and SD females, in a dose-dependent fashion, even at the lowest dose tested.¹⁰
- Pregnant F344 rats appear more sensitive than SD and LE rats to atrazine-induced full-litter resorption (FLR). Gavage-dosed F344 rats showed FLR at 50 mg/kg, whereas in SD and LE rats, FLR occurred at 200 mg/kg.¹¹
- While both male and female Wistar rats responded to atrazine-treatment with delayed puberty, males responded at much lower treatment doses. In the female, oral gavage of 50-200 mg/kg atrazine at postnatal day 22-41 resulted in delayed vaginal opening (puberty), in a dose-dependent manner.¹² In male rats, preputial separation was significantly delayed following treatment with 12.5, 50, 100, 150, and 200 mg/kg atrazine administered by gavage (PND 23-53), resulting in delayed puberty.¹³

MECHANISM(S) OF ACTION LEAVES OPEN POSSIBILITY OF CARCINOGENICITY IN HUMANS

At the time of the IARC evaluation (1999) and the previous EPA SAP evaluation (2000),¹⁴ it was hypothesized, in the absence of supporting data, that the mechanism by which atrazine induced mammary tumors in SD rats, attenuation of the leutenizing hormone surge, was not directly relevant to humans. There are now some *in vitro* and animal studies suggesting that atrazine may also induce aromatase activity, leading to conversion of testosterone to estrogen, resulting in a

decrease in testosterone, and increase in estrogen.^{15 16 17} While the evidence in the published literature is not complete, it suggests that atrazine has at least two distinct mechanisms of toxicity, and that further research may reveal others. The possibility of multiple mechanisms of action for atrazine suggests that we do not yet understand the mechanism of atrazine toxicity sufficiently, and we must therefore consider all findings in animals, including tumors in SD rats, to be relevant to humans.

Disruption of LH and prolactin levels (whole animal studies):

- Atrazine alters LH and prolactin serum levels in LE and SD female rats by disrupting the hypothalamic control of pituitary-ovarian function. Interestingly, while atrazine suppressed pituitary LH and prolactin release, it did not affect pituitary TSH and FSH release.¹⁸
- Atrazine inhibited suckling-induced prolactin release in the pups of atrazine-treated dams (12.5 mg/kg gavage, twice daily). In this study, atrazine was not transferred through lactation to the pups.¹⁹

Activation of aromatase (studies in human-derived cell cultures):

- Aromatase is the rate-limiting step enzyme in the conversion of androgens to estrogen. Atrazine, simazine, and propazine induced aromatase (CYP19) activity in the H295R human-derived adrenocortical carcinoma cell line. Aromatase was induced in a dose-dependent manner, from 1-30 μ M atrazine (note: atrazine formula weight=215, so that a 1 μ M atrazine solution= 215 μ g/L=215 ppb).²⁰ Atrazine induced aromatase to a maximum of 2.5-fold above background. This finding was confirmed in subsequent studies, which also demonstrated that atrazine induced cAMP in the same experimental system.²¹

On the topic of mechanistic data used for evaluation of carcinogenicity, scientists from the National Institute of Environmental Health Sciences (NIEHS) recommended:

When formulating guidelines for acceptance of mechanistic hypotheses, we expect regulatory agencies to require rigorous testing and validation before using incomplete data sets to downgrade the categorization of chemical carcinogens. Such guidelines must also address whether differences in mechanistic events among species are truly qualitative rather than quantitative in nature. For quantitative differences, the guidelines should also require information on the range of parameter variability in exposed humans so that sensitive subpopulations are not ignored in these categorizations. The issue is not singularly the adequacy of mechanistic or epidemiologic evidence, but certainty for protecting public health.²²

NIEHS senior scientist James Huff writes that “serious public health consequences might follow in the occupational, environmental, and public health communities if decision-making bodies like EPA rely on untested mechanistic hypotheses that are later shown experimentally to be incorrect. On the use of mechanistic data for evaluating chemical carcinogens, there is a continuing need for rigorous testing of mechanistic hypotheses. Hurried and unbridled acceptance and use of mode-of-action is premature and not good for public health. There appears to be a rush to accept MoA without adequate testing of posed mechanisms, especially for those used for discounting extrapolation of cancer findings from animals to humans” (emphasis added).²³ *We urge the Scientific Advisory Panel to consider the findings in all animal studies to be relevant, when making their evaluation of atrazine carcinogenicity.*

ATRAZINE MAY BE CARCINOGENIC THROUGH DISRUPTION OF HORMONE ACTIVITY, AND MAY BE OF PARTICULAR CONCERN FOR EARLY LIFE STAGES: atrazine causes events generally known to be associated with tumor formation

EPA has released its 2003 Draft Final Cancer Guidelines and Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens. This supplemental guidance was reviewed by the Scientific Advisory Board (SAB) in June of this year. The SAB recommended that the EPA make their guidance even more protective of early-life stage exposures to endocrine disrupting chemicals. The SAB recognized that “[i]t is likely that early-life stages have windows of susceptibility to carcinogens acting through endocrine disruption”, providing as examples diethylstilbestrol, tamoxifen, and others (SAB report, June 20, 2003).²⁴ In summary, the SAB stated that there is reason to believe that hormonal agents can be more potent carcinogens when exposure occurs in early-life stages than in later-life stages alone.

There is evidence from multiple animal species, both sexes, and multiple rodent strains, that atrazine acts as an endocrine disruptor. Atrazine has been shown to attenuate the LH surge and may increase aromatase-induced conversion of testosterone to estrogen. In addition, male²⁵ and female²⁶ Wistar rats displayed delayed puberty following atrazine treatment. In Fischer rats, atrazine treatment resulted in reduced sperm motility.²⁷ Treatment of nursing Wistar dams with atrazine suppressed suckling-induced prolactin release, leading to lateral prostate inflammation in the suckling male offspring.²⁸ Frogs exposed to atrazine under laboratory conditions displayed gonadal abnormalities, including hermaphroditism.^{29 30 31 32} We therefore suggest that there is ample evidence in multiple strains and species of animals that atrazine causes events generally known to be associated with tumor formation, and therefore likely that atrazine is a carcinogen, to which early life stages (in utero exposures) are especially vulnerable.

Atrazine exposure during development predisposes to later life cancers

Published data by EPA scientists demonstrate in animal studies that exposure to atrazine during development of Long Evans (LE) rats increases the risk of developing cancer later in life. LE rats were exposed in utero to atrazine, followed by challenge with the carcinogen dimethylbenz[a]anthracene.³³ Atrazine-exposed pups demonstrated delayed mammary bud outgrowth, followed by an increase in multiplicity and volume of tumors after exposure to the carcinogen, compared to non-atrazine treated controls. In addition, the atrazine-exposed pups showed an increase in organ pathology, compared with controls. Authors suggest that by delaying mammary gland development, gestational atrazine exposure increases the susceptibility of the LE female to carcinogen, perhaps, by extending the period of vulnerability.³⁴

Atrazine disrupts hormonal pathways in multiple species

Atrazine is a multi-species endocrine disruptor, with demonstrated effects in several species of mammals, amphibians, and other aquatic organisms. While no two studies are identical, there are sufficient data from robust, well-designed studies to demonstrate that atrazine is a multi-species, multi-site endocrine disruptor. The published literature is consistent in demonstrating that atrazine may disrupt normal hormonal pathways, resulting in disruption of reproductive hormones and reproductive cycles. All results summarized below are of statistical significance, and are reported by the study authors.

In rats:

- Atrazine disrupts the normal progression of sexual development in experimental mammals. When nursing rats were treated with atrazine the male offspring developed prostate gland inflammation³⁵ (note, this study was done by EPA staff scientists). It is not currently known if prostatitis will proceed to prostate cancer.

- Treatment of Wistar male and female rats with atrazine from weaning until puberty resulted in delayed sexual maturity. In the female, oral gavage of 50-200 mg/kg atrazine at postnatal day 22-41 delayed vaginal opening (puberty), in a dose-dependent manner.³⁶ In male rats preputial separation was significantly delayed following treatment with 12.5, 50, 100, 150, and 200 mg/kg atrazine administered by gavage (PND 23-53), resulting in delayed puberty.³⁷
- In juvenile rat males administered atrazine by gavage at 50 mg/kg/day acutely (PND 46-48) and chronically (PND 22-48), serum and intratesticular levels of testosterone were reduced significantly. Further work by the same authors in cell culture systems demonstrated that atrazine acted by inhibiting Leydig cell testosterone production.³⁸
- Atrazine has been shown to reduce sperm motility in exposed Fischer rats.³⁹ Animals were treated with 60 and 120 mg/kg atrazine administered twice weekly by intraperitoneal (i.p.) injection over a period of 60 days. The authors report that testicular sperm number in atrazine-treated groups increased with the treatment time due to reduced sperm motility.

In pigs:

- Delayed estrus was demonstrated in female pigs fed atrazine.⁴⁰ Pigs were fed atrazine-laced feed (1 mg/kg/day) for 19 days prior to estrus, resulting in abnormally reduced serum estradiol-17 β levels, and delayed estrus.

In other aquatic species:

- In an experimental study of alligators, 14 ppm atrazine induced aromatase activity in male hatchlings, although testicular differentiation was not altered.⁴¹
- Tiger salamander metamorphosis was affected by sublethal concentrations of atrazine, but, most interesting, the response differed at different concentrations.⁴² Authors collected eggs from the wild, and exposed them under controlled laboratory conditions to 0, 75, and 250 μ g/L (ppb). At the lower concentration, development was delayed, but size and weight were not affected. At the higher concentration, development progressed at a normal rate, but size and weight were reduced.

In multiple species of frogs, both in the wild and under controlled laboratory conditions:

Atrazine acts in amphibians to disrupt reproductive organ development. All results reported below are of statistical significance, and are reported by the study authors:

- Published studies by Tavera-Mendoza et al report that following exposure to water concentrations of 21 ppb (μ g/L) atrazine for 48 hours under controlled laboratory conditions, *Xenopus laevis* males displayed testicular resorption, resulting in gonadal dysgenesis (small underdeveloped testis with decreased germ cell numbers).⁴³ In females, exposure during ovary differentiation resulted in a decline in primary and secondary oögonia. In males, the same treatment resulted in a significant reduction in overall size of testes, in the numbers of primary spermatogonial cell nests (germ cells), and in the numbers of nursing cells that provide nutritive support for the developing germ cells.⁴⁴ Significant testicular resorption or incomplete development of testes was also reported. The authors suggest that reproductive development and hormonal regulation is highly conserved among vertebrates, suggesting that these findings raise general concern for wildlife and humans.

- Syngenta-funded researchers treated *Xenopus laevis* frog larvae throughout development, under laboratory controlled conditions.⁴⁵ They reported an increase in intersex animals at 25 µg/L atrazine, but no effects at lower concentrations (1, 10 µg/L).
- In field studies in wild *Rana pipiens* frogs, Tyrone Hayes et al reported retarded gonadal development and testicular oogenesis (hermaphroditism) in males at all sites where water-concentrations of atrazine was measured in excess of 0.1 µg/L.^{46 47} It is interesting that Hayes reports that under laboratory controlled conditions, low doses (0.1 ppb) of atrazine were more toxic than higher doses (25 ppb) to testicular development.⁴⁸ Hayes points out that this is consistent with the action of other endocrine disruptors, and that even estradiol treatment has different effects at different concentrations.
- Preliminary findings of a study funded by Syngenta found hermaphroditic *Bufo marinus* (cane toads) in sugarcane fields treated with atrazine, but no hermaphroditism at reference sites free of atrazine.⁴⁹ Males in contaminated areas had female-typical skin coloration, had measurable vitellogenin in the plasma and some had eggs.⁵⁰ Most interesting, the study design had a built in concentration-gradient, finding that frogs closer to the treated fields had more abnormal reproductive effects than frogs collected farther away. It was reported that this work “lends credence to University of Berkeley endocrinologist Tyrone Hayes’ hypothesis that atrazine is affecting sexual development of amphibians,” and Syngenta-funded researcher Tim Gross was cited saying, “the findings are consistent with the previous work of both Hayes and (Syngenta-sponsored) Texas Tech experimental toxicologist James Carr, ‘Carr finds an effect at atrazine concentrations that are similar to what we see in the field and to what we think the toads are exposed.’ ”⁵¹

EVIDENCE FOR CARCINOGENICITY IN HUMANS

Hispanic farm workers show increased prostate cancer associated with high atrazine exposure

An epidemiology study published this spring reports that Hispanic farm workers with elevated exposure to triazine herbicides (simazine) experienced elevated risk of prostate cancer compared to workers with lower levels of exposure.⁵² EPA considers simazine and atrazine to share a common mechanism of toxicity.⁵³ Risk of prostate cancer was increased approximately 50-80% in the higher use quartiles (29 cases, OR=1.81, 95%CI=.93-3.53 at the highest quartile). While not statistically significant, the authors report that the relationship was statistically significant in men with more advanced disease at diagnosis (N=94, OR=2.16, 95%CI=1.15-4.04). The authors concluded that, “Hispanic farm workers with relatively high levels of exposure to . . . triazine herbicides (simazine) experienced elevated risk of prostate cancer compared to workers with lower levels of exposure.”

Triazine exposures associated with ovarian cancer in exposed women

An epidemiology study by Donna et al found an association between triazine exposure and ovarian cancer among exposed women.⁵⁴ The authors report that women previously exposed to triazines showed a significant relative risk of 2.7 for ovarian neoplasms. Although none of the doses could be quantified for the study subjects, the authors suggest that risk trends for duration and probability of exposure both favor of the plausibility of the association.

The NCI reports an association between female pesticide applicators in the Midwest and ovarian cancer

The National Cancer Institute Agriculture Health Study reports a significant association between Midwest female pesticide applicators and ovarian cancer. The effect is observed in both Iowa and North Carolina, where large amounts of atrazine are applied; Iowa applies 7-8 million pounds of atrazine annually, and North Carolina applied approximately 500,000 pounds of atrazine in 2001.⁵⁵ The findings of elevated ovarian cancer in female applicators are statistically significant when the cases from Iowa and North Carolina are combined (8 observed cases/ 1.9 expected cases).⁵⁶ These findings were reported in conference proceedings, and are being published in the Scandinavian Journal of Work Environment and Health.

Industry-sponsored study find workers in the atrazine manufacturing plant have elevated prostate and other cancers; no data provided for possible PSA confounding

EPA provides a review of an occupational epidemiology study of workers in an atrazine manufacturing plant in St. Gabriel, Louisiana. EPA concludes that the study was “insufficiently large and has limitations that prevent ruling out atrazine as a potential contributor to the increase observed.” (IRED at 49). In other words, the study fails to disprove the apparent link between atrazine exposure and increased cancer cases among workers. This is supported by further suggestive evidence, acknowledged by EPA in the Interim Reregistration Eligibility Decision (IRED) for atrazine (p. 49): “atrazine has also been tied to inflammation of the prostate in laboratory animals and changes in testosterone at high doses”; “other cancers besides prostate were found to have an elevated, though not statistically significant, increase in risk at the St. Gabriel plant”; “other studies have suggested an increased risk for ovarian, breast, and other cancers, including non-Hodgkin’s lymphoma.” Although the study is underpowered, insufficient statistical power usually results in an underestimate of the magnitude of an association between an exposure and disease.

The findings of the Syngenta/Novartis study of the atrazine manufacturing plant are presented in the Table below. All data is from the company study submitted to the EPA. Note that the company divided the cohort of workers into active and inactive employees, to designate whether they were currently employed by the plant, or former employees. The cohort was also divided into company and contract employees. Note that the excess in prostate cancers (11 v. 1.8) is in the active company employees, the same group that also received intensive PSA-screening. The study authors do not provide data on the levels of PSA-screening in the reference population, or provide adequate data to show that the elevation in observed prostate cancers among active employees is due to more aggressive screening.

Table 1: Observed/expected number of prostate cancers, by employee group, 1985-1999. Expected values are derived from comparison with the industrial corridor.⁵⁷

	ACTIVE EMPLOYEES	INACTIVE	TOTAL
COMPANY	11/1.8 (SIR=613, CI=306-1096)	3/3.7	14/5.5
CONTRACT	1/1.1	2/3.0	3.0/4.1
TOTAL	12/2.9	5/5.6	17/9.5

The study authors published their findings in the November issue of Journal of Occupational and Environmental Medicine (JOEM). In the article, it is mentioned in passing that, “...11 cases occurred among men who were actively working when diagnosed, compared to an expected number of about 1.8 (SIR=613, CI=306-1096).”⁵⁸ As J. Sass (NRDC) points out in a published letter to the editor of JOEM, this significant elevation in risk is not so easily explained away by the authors’ hypothesis that PSA screening may be responsible for increased detection.⁵⁹ These additional follow-up data do not reappear in any tables, or in the introduction, discussion,

conclusion, or abstract. Although the authors note the follow-up 1998-1999 prostate cancers, they do not provide any similar follow-up data for other cancers, despite marginal elevations in the 1985-1997 data (digestive system, bladder, lymphohematopoietic cancer, non-Hodgkin's lymphoma). Elevations in cancers of these other sites are not attributable to a PSA-testing bias, and bear further study.

UNDER THE 2003 DRAFT CANCER GUIDELINES, ATRAZINE IS A “LIKELY” HUMAN CARCINOGEN

Declaring chemicals ‘not carcinogenic to humans’ requires validation, not speculation

The decision by EPA to classify atrazine as “not likely” a human carcinogen is inconsistent with the 2003 Draft Final Cancer Guidelines, and with the IARC criteria. The IARC states that the classification of “not a human carcinogen” requires a wealth of data, including multiple, mutually consistent, adequately powered studies covering the full range of human exposures that exclude with reasonable certainty bias, confounding, and chance to provide individual and pooled estimates of risk near unity with narrow confidence intervals.⁶⁰ As NIEHS scientists state, “declaring chemicals ‘not carcinogenic to humans’ requires validation, not speculation.”⁶¹ Importantly, IARC cautions that latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity (workers in the St. Gabriel study have a median of 18 years follow-up). *In no way should the absence of data be considered evidence of an absence of carcinogenicity.*

The 2003 Draft Final Cancer Guidelines provide a framework for “judging whether available data support a mode of carcinogenic action hypothesized for an agent.”⁶² This framework incorporates the criteria for causality used in epidemiological studies, as stated by Bradford Hill (1965), with subsequent modifications. The author and those who use these criteria understand that each criterion support the determination of causality, and the more criteria that are satisfied, the stronger the evidence for causality. However, it is not necessary, and not likely, that all criteria are satisfied to demonstrate causality.⁶³ Further, the Guidelines remind the user that support for one mode of action does not limit the possibility of other modes of action. Rather, the Agency is obligated to consider the highly likely possibility of other modes of action that may be consistent with tumor formation in humans. For example, atrazine has been shown in animals and in human-derived cell cultures to stimulate aromatase activity, resulting in conversion of testosterone to estrogen. Might this mode of action cause or contribute to observed mammary tumors in male atrazine-exposed animals? The possibility, coupled with all existing experimental and epidemiological data suggest that atrazine is more appropriately a “likely” human carcinogen, according to the 2003 Guidelines.

SUMMARY

We respectfully suggest to the members of the Scientific Advisory Panel that atrazine fulfills the criteria for a “likely” human carcinogen:

- a) evidence of cancer in laboratory animals, in two species,
- b) demonstrated endocrine disruption in atrazine-exposed laboratory animals, in multiple species, which may predispose an atrazine-exposed fetus or neonate to cancer later in life
- c) evidence that exposure to atrazine during development predisposes laboratory animals to developing cancer later in life, and
- d) evidence of endocrine and cancer effects in atrazine-exposed humans.

It is the role of EPA to regulate chemicals so as to protect human health and the environment, not commercial interests.

Thank you for the opportunity to provide comments on this important agricultural chemical.

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*The signatories' institution is given for identification purposes only and does not constitute an endorsement on the part of the institutions of information contained in this letter.

- 1 EPA NCEA website: <http://cfpub1.epa.gov/ncea/raf/recordisplay.cfm?deid=55868>
- 2 Draft report of the SAB. Supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogenesis (SCACS) review panel. June 20, 2003. P. 5. Available electronically at <http://www.epa.gov/sab/pdf/sgacsdfrpt062003.pdf>
- 3 Eldridge JC, Tennant MK, Wetzel LT, Breckenridge CB, Stevens JT. Factors affecting mammary tumor incidence in chlorotriazine-treated female rats: hormonal properties, dosage, and animal strain. *Environ Health Perspect.* 1994 Dec;102 Suppl 11:29-36.
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- 4 Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect.* 2003 Apr;111(4):389-94.
- 5 Fenton SE, Davis CC. 2002. Atrazine exposure in utero increases dimethylbenz[a]anthracene-induced mammary tumor incidence in long evans offspring. *Society of Toxicology Abstr.*, p. 185
- 6 Donna A, Betta PG, Robutti F, Bellingeri D. Carcinogenicity testing of atrazine: preliminary report on a 13-month study on male Swiss albino mice treated by intraperitoneal administration. *G Ital Med Lav.* 1986 May-Jul;8(3-4):119-21.
- 7 Cooper RL, Stoker TE, Goldman JM, Parrish MB, Tyrey L. Effect of atrazine on ovarian function in the rat. *Reprod Toxicol.* 1996 Jul-Aug;10(4):257-64.
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- 9 Narotsky MG, Best DS, Guidici DL, Cooper RL. Strain comparisons of atrazine-induced pregnancy loss in the rat. *Reprod Toxicol.* 2001 Jan-Feb;15(1):61-9.
- 10 Cooper RL, Stoker TE, Tyrey L, Goldman JM, McElroy WK. Atrazine disrupts the hypothalamic control of pituitary-ovarian function. *Toxicol Sci.* 2000 Feb;53(2):297-307.
- 11 Narotsky MG, Best DS, Guidici DL, Cooper RL. Strain comparisons of atrazine-induced pregnancy loss in the rat. *Reprod Toxicol.* 2001 Jan-Feb;15(1):61-9.
- 12 Laws SC, Ferrell JM, Stoker TE, Schmid J, Cooper RL. The effects of atrazine on female wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. *Toxicol Sci.* 2000 Dec;58(2):366-76.
- 13 Stoker TE, Laws SC, Guidici DL, Cooper RL. The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol Sci.* 2000 Nov;58(1):50-9.

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